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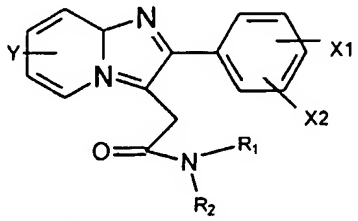
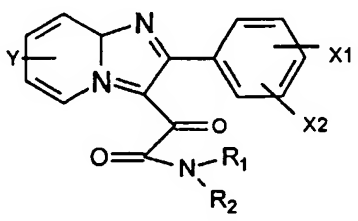
(54) Title: PROCESS FOR THE PREPARATION OF IMIDAZOPYRIDINES



(1)

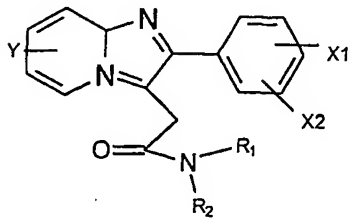


(6)

(57) Abstract: A compound of general formula (1), in which Y denotes hydrogen, a halogen or a C_{1-4} alkyl group X_1 and X_2 denote, independently of each other, hydrogen, a halogen or a C_{1-4} alkoxy, C_{1-6} alkyl, CF_3, CH_3S CH_3SO_2 or NO_2 group and R_1 and R_2 denote independently of each other, hydrogen or a C_{1-5} alkyl group, with the proviso that R_1 and R_2 do not both denote hydrogen, or a salt thereof is prepared by a multi-step process, the last step of which comprises reducing a compound of general formula (6), in which Y, X_1, X_2, R_1 and R_2 are as defined above with an appropriate reducing agent, such as Zn, and, if desired, converting the compound of formula (1) thus obtained, into a salt. The product of this process are known to have useful pharmacological properties, e.g. as anxiolytics.

PROCESS FOR THE PREPARATION OF IMIDAZOPYRIDINES

The present invention relates to a process for preparing imidazopyridines of the general formula (1)



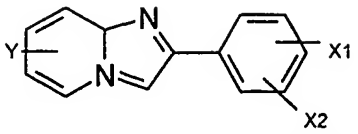
(1)

in which:
Y denotes hydrogen, a halogen or a C_{1-4} alkyl group,
X_1 and X_2 denote, independently of each other, hydrogen, a halogen or a C_{1-4} alkoxy, C_{1-6} alkyl, CF_3, CH_3S, CH_3SO_2 or NO_2 group and
R_1 and R_2 denote, independently of each other, hydrogen or a C_{1-5} alkyl group, with the proviso that R_1 and R_2 do not both denote hydrogen,
or salts thereof.

The products of this process are known to have useful pharmacological properties, e.g. as anxiolytics, see European Patent No. 0 050 563. A process for preparing compounds of formula 1 is described in US Patent No. 4,794,185, Dec. 12, 1988.

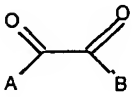
The present invention relates to a more efficient process for preparing compounds of formula (1).

In accordance with the present invention, compounds of the general formula (1) can be prepared by reacting a compound of the general formula (2)



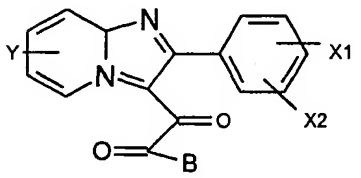
(2)

in which Y, X_1 and X_2, are as defined above
with a compound of the general formula (3)



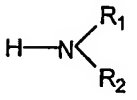
(3)

in which:
A denotes a halogen and B denotes a halogen, a C_{1-4} alkoxy group or an NR_1R_2 group in which R_1 and R_2 are as defined above
to form a compound of the general formula (4)



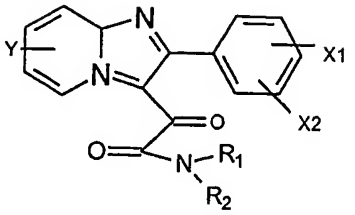
(4)

in which Y, X_1, X_2 and B are as defined above,
and, if B denotes a halogen or a C_{1-4} alkoxy group, reacting the compound of the general formula (4) with a compound of the general formula (5)



(5)

in which R_1 and R_2 are as defined above to form a compound of the general formula (6)



(6)

in which Y, X_1, X_2, R_1 and R_2 are as defined above.

To form a compound of formula (1), the compound of formula (6) can be treated with a reducing agent If desired, the compound of formula (1) thus obtained is converted into a salt.

It will be appreciated that if in formula (3) B denotes an NR_1R_2 group in which R_1 and R_2 are as defined above, compound (6) instead of compound (4) is formed directly by reaction of compound (2) with compound (3).

As set forth above compound (6) is prepared by reacting an imidazopyridine of formula (2) with an oxalic acid derivative of formula (3). This reaction is conveniently carried out in an aprotic organic solvent, for example n-hexane, cyclohexane, acetonitrile, acetone, ethylacetate, toluene, methyl tert. butyl ether or mixtures of these solvents, preferably a mixture of cyclohexane with toluene, at a temperature range from 0-100° C, preferably from 0-10°C, and in the presence of an organic base, for example tertiary alkylamines, pyridine or substituted pyridines, preferably pyridine. If in formula (3) B denotes a halogen or a C_{1-4} alkoxy group, the product (4) thus obtained is subsequently reacted with a primary or secondary amine of formula (5), conveniently at a temperature range from 0-100°C, preferably from 30-40°C. If in formula (3) B denotes an NR_1R_2 group, the reaction of compound (2) with compound (3) directly yields a compound of formula (6) instead of compound (4), and no intervening treatment with a compound of formula (5) is necessary.

The compound of formula (6) thus obtained is then reacted with an appropriate reducing agent to form compound (1). This reaction is conveniently carried out in a polar aprotic solvent, for example pyridine, dimethylformamide or acetonitrile, preferably pyridine, in the presence of an organic acid, for example acetic acid, formic acid or toluenesulfonic acid, preferably acetic acid, and of an acylating agent, for example acetic anhydride or acetylchloride, preferably acetic anhydride, at a temperature range from 25-75°C, preferably from 50-55°C. A suitable reducing agent is, for example, Zn.

The compounds of the general formula (6) and their preparation also form part of the present invention.

The following examples illustrate the invention in greater detail.

EXAMPLE 1

Preparation of 6-methyl-N,N-dimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-glyoxyacetamide, compound (6)

To a slurry of 10.0 g (45 mmol) of 6-methyl-N,N-dimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine in a mixture of 20.0 g of toluene and 28.0 g of cyclohexane were added 8.6 (0.068 mmol) of oxalylchloride within 15 minutes at 0-5°C. 3.6 g (45 mmol) of pyridine were added within 5 minutes at 0-5°C. The resulting slurry was heated to 65-70°C and stirred for 2 hours. Then it was cooled to 30-35°C and 8.4 g (187 mmol) of dimethylamine were introduced. To the slurry were added 26.0 g of water and 2.3 g of isopropanol. The product was isolated by filtration to afford the title compound in 80 % yield.

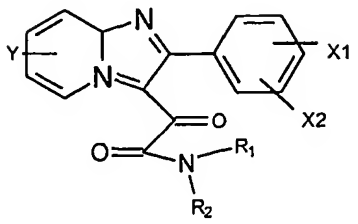
EXAMPLE 2

Preparation of N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-yl]acetamide, compound (1)

To a slurry of 150.0 g (0.467 mol) of 6-methyl-N,N-dimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-glyoxyacetamide and 105.0 g (1.605 mol) of zinc powder in 443.0 g of pyridine was added a solution of 94.0 g (0.920 mol) of acetic anhydride in 472.5 g of acetic acid within 20 - 25 minutes at a temperature below 45°C. The suspension was then heated to 50-55°C and stirred for 25-30 hours. Unreacted zinc was filtered off and the filtrate was subjected to a vacuum distillation. To the remaining oil 455.0 g of 25% aqueous ammonia solution were added. The precipitated solid was collected by filtration and purified by recrystallization in 800.0 g of methylisobutylketone. The title compound was afforded in 65.6 % yield.

CLAIMS:

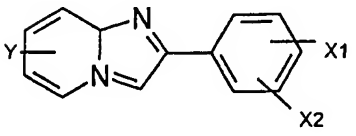
1. A process for preparing compounds of the general formula (6)



(6)

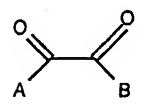
in which:
Y denotes hydrogen, a halogen or a C_{1-4} alkyl group.
X_1 and X_2 denote, independently of each other, hydrogen, a halogen or a C_{1-4} alkoxy, C_{1-6} alkyl, CF_3, CH_3S, CH_3SO_2 or NO_2 group and
R_1 and R_2 denote, independently of each other, hydrogen or a C_{1-5} alkyl group, with the proviso that R_1 and R_2 do not both denote hydrogen,

which process comprises reacting a compound of the general formula (2)



(2)

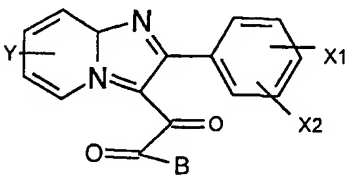
in which Y, X_1 and X_2, are as defined above
with a compound of the general formula (3)



(3)

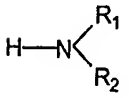
in which:

A denotes a halogen and B denotes a halogen, a C_{1-4} alkoxy group or an NR_1R_2 group in which R_1 and R_2 are as defined above
to form a compound of the general formula (4)



(4)

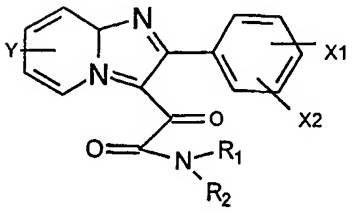
in which Y, X_1 X_2 and B are as defined above
and, if B denotes a halogen or a C_{1-4} alkoxy group, reacting the compound of formula (4) with a compound of the general formula (5)



(5)

in which R_1 and R_2 are as defined above.

2. A compound of the general formula (6)

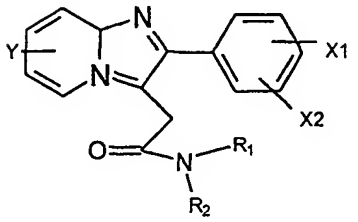


(6)

in which:
Y denotes hydrogen, a halogen or a C_{1-4} alkyl group
X_1 and X_2 denote, independently of each other, hydrogen, a halogen or a C_{1-4} alkoxy, C_{1-6} alkyl, CF_3, CH_3S, CH_3SO_2 or NO_2 group and

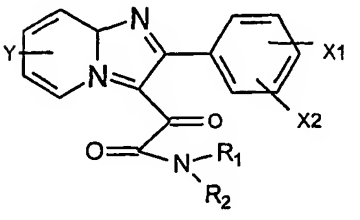
R_1 and R_2 denote independently of each other, hydrogen or a C_{1-5} alkyl group, with the proviso that R_1 and R_2 do not both denote hydrogen.

3. A process for preparing a compound of the general formula (1)



(1)

in which:
Y denotes hydrogen, a halogen or a C_{1-4} alkyl group
X_1 and X_2 denote, independently of each other, hydrogen, a halogen or a C_{1-4} alkoxy, C_{1-6} alkyl, CF_3, CH_3S CH_3SO_2 or NO_2 group and
R_1 and R_2 denote independently of each other, hydrogen or a C_{1-5} alkyl group, with the proviso that R_1 and R_2 do not both denote hydrogen,
or a salt thereof
which process comprises reducing a compound of the general formula (6)



(6)

in which Y, X_1, X_2, R_1 and R_2 are as defined above
with an appropiate reducing agent and, if desired, converting the compound of formula (1) thus obtained into a salt.

4. A process according to claim 3 wherein the reducing agent is Zn .

5. A process according to claim 3 or claim 4 wherein the reduction is carried out in pyridine, dimethylformamide, dimethylacetamide, acetonitrile or a derivative of any of these, in the presence of acetic acid, formic acid or toluenesulfonic acid and of an acylating agent.

6. A process according to claim 5 wherein the acylating agent is acetic anhydride or acetylchloride.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 00/08021

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 A61K31/437 A61P25/22 //(C07D401/04,235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 382 938 A (KAPLAN JEAN-PIERRE ET AL) 10 May 1983 (1983-05-10) column 2, reaction scheme column 9, Table, compounds 91, 92 claim 1 & EP 0 050 563 A 28 April 1982 (1982-04-28) cited in the application	1-6
A	US 4 794 185 A (ROSSEY GUY ET AL) 27 December 1988 (1988-12-27) column 2, line 1 - line 3 column 7, Appendix claims	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2001	08/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoepfner, W

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/EP 00/08021

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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